One of the arguments against the findings of conventional population studies is the fact that smokers are self-selected and that other factors may be involved in the causation of IHD.

It has been maintained by Friedman & Rosenman (1972) that persons with a particular behavior pattern, type A, characterized by aggressiveness, striving and time consiousness, more often develop myocardia infarction than the more placid type B; and the type A person is also more likely to be a heavy smoker.

Questionnaire studies on the Swedish as well as the U.S. Twin Registries disclosed an association for males between smoking and angina pectoris when the results were analysed on a non-pair basis, but comparisons within smoking discordant pairs showed no association with smoking for the MZ twins (report from symposium in San Juan, Puerto Rico, 1969). These results are supported by a clinical study on 196 smoking discordant pairs (Lundman, 1966) from the Swedish Twin Registry, no difference being found with regard to IHD within the smoking discordant pairs.

Material: see Chapter I.

Methods

Information about smoking habits was obtained from questionnaire replies received in 1967/1970. If the twins had answered in 1967 as well as 1970, the latter report was used.

Results

Smoking habits in the male and female death discordant pairs accordin to the questionnaires are shown in Tables 26-28. When present and former smokers are combined (Table 28), the percentage distribution of male smokers is somewhat, but not significantly, higher for the IHD compared to the not-IHD death discordant pairs. Of the male twins who died from IHD, 83 % were smokers as against 85 % of their surviving co-twins, while 76 % of those who died from other causes than IHD were smokers compared with 72 % of their surviving co-twins. The corresponding figures for cigarette smokers in the IHD death discorda pairs are 50 % and 55 % compared to 40 % and 52 % among the not-IHD death discordant pairs. Nor are these differences significant.

There were more former cigarette smokers (Table 26) among the deceased male twins than the surviving co-twins, especially among those who died from IHD.

With respect to zygosity groups (Table 28), 60 % (6 of 10) of the

Table 26. Smoking habits in male death discordant pairs according to earlier questionnaires. Percentage distribution.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Non smokers																

Table 26. Smoking habits in male death discordant pairs according to earlier questionnaires. Percentage distribution.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Non smokers	10	20	20	16	20	0	18	15	20	16	26	19	0	0	24	18
Total present smokers	40	80	52	68	60	60	50	70	56	60	52	67	100	100	54	65
Total cigarette smokers	30	80	24	24	60	60	30	43	12	32	26	36	100	100	22	35
1-10 cigarettes daily	20	30	16	12	40	20	20	18	8	28	14	21	100	0	13	24
⩾11 cigarettes daily	10	50	8	12	20	40	10	25	4	4	12	14	0	100	9	12
Cigar and/or pipe	10	0	28	44	0	0	20	28	44	28	26	31	0	0	32	29
Total former smokers	50	0	28	16	20	40	33	15	24	24	21	14	0	0	22	18
Total cigarette smokers	30	0	16	12	20	40	20	13	24	20	14	14	0	0	18	16
1-10 cigarettes daily	10	0	16	8	20	20	15	8	16	16	10	14	0	0	12	15
⩾11 cigarettes daily	20	0	0	4	0	20	5	5	8	4	5	0	0	0	6	1
Cigar and/or pipe	20	0	12	4	0	0	13	3	0	4	7	0	0	0	4	1
Total number	10	10	25	25	5	5	40	40	25	25	42	42	1	1	68	68

D=Deceased twin; S=Surviving co-twin

Table 27. Smoking habits in female death discordant pairs according to earlier questionnaires. Percentage distribution.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Non smokers	75	50	78	67	-	-	76	59	70	77	85	79	50	100	79	79
Total present smokers	25	13	11	33	-	-	18	24	30	23	15	17	50	0	21	19
Total cigarette smokers	25	13	11	33	-	-	18	24	27	23	15	17	50	0	20	19
1-10 cigarettes daily	13	13	11	11	-	-	12	12	20	23	10	10	50	0	15	15
≥11 cigarettes daily	13	0	0	22	-	-	6	12	7	0	4	6	0	0	5	4
Cigar and/or pipe	0	0	0	0	-	-	0	0	3	0	0	0	0	0	1	0
Total former smokers	0	38	11	0	-	-	6	18	0	0	0	4	0	0	0	3
Total cigarette smokers	0	38	11	0	-	-	6	18	0	0	0	2	0	0	0	1
1-10 cigarettes daily	0	25	11	0	-	-	6	12	0	0	0	2	0	0	0	1
≥11 cigarettes daily	0	13	0	0	-	-	0	6	0	0	0	0	0	0	0	0
Cigar and/or pipe	0	0	0	0	-	-	0	0	0	0	0	2	0	0	0	1
Total number	8	8	9	9	0	0	17	17	30	30	48	48	2	2	80	80

D=Deceased twin; S=Surviving co-twin

Table 28. Smoking habits in male and female death discordant pairs according to earlier questionnaires with present and former smokers combined. Percentage distribution.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S

Table 28. Smoking habits in male and female death discordant pairs according to earlier questionnaires with present and former smokers combined. Percentage distribution.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
MALES:																
Non smokers	10	20	20	16	20	0	18	15	20	16	26	19	0	0	24	18
Total smokers	90	80	80	84	80	100	83	85	80	84	74	81	100	100	76	72
Total cigarette smokers	60	80	40	36	80	100	50	55	36	52	41	50	100	100	40	52
1-10 cigarettes daily	30	30	32	20	60	40	35	25	24	44	24	36	100	0	25	38
⩾11 cigarettes daily	30	50	8	16	20	60	15	30	12	8	17	14	0	100	15	13
Cigar and/or pipe	30	0	40	48	0	0	33	30	44	32	33	31	0	0	37	31
Total number	10	10	25	25	5	5	40	40	25	25	42	42	1	1	68	68
FEMALES:																
Non smokers	75	50	78	67	-	-	77	59	70	77	85	79	50	100	79	79
Total smokers	25	50	22	33	-	-	24	41	30	23	15	21	50	0	21	21
Total cigarette smokers	25	50	22	33	-	-	24	41	30	23	15	19	50	0	20	20
1-10 cigarettes daily	13	38	22	11	-	-	18	35	30	23	15	19	50	0	15	20
⩾11 cigarettes daily	13	13	0	22	-	-	6	18	7	0	4	6	0	0	3	4
Cigar and/or pipe	0	0	0	0	-	-	0	0	3	0	0	2	0	0	1	1
Total number	8	8	9	9	0	0	17	17	30	30	48	48	2	2	80	80

D=Deceased twin; S=Surviving co-twin

Table 29. Distribution of death discordant male twin pairs according to concordance/discordance with respect to smoking habits (present and former smokers combined).

		Deceased twin															
		IHD								not IHD							
		MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
		NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM
Surviving co-twin	NS	1	1	2	2	0	0	3	3	4	0	4	4	0	0	8	4
	SM	0	8	3	18	1	4	4	30	1	20	7	27	0	1	8	48

Table 30. Distribution of death discordant male twin pairs according to concordance/discordance with respect to cigarette habits (present and former smokers combined).

		Deceased twin															
		IHD								not IHD							
		MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
		NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM
Surviving co-twin	NS	1	1	2	1	0	0	3	2	4	0	4	3	0	0	8	3
	SM	0	8	1	12	1	4	2	24	1	14	5	20	0	1	6	35

Table 31. Distribution of death discordant female twin pairs according to concordance/discordance with respect to smoking habits (present and former smokers combined).

		Deceased twin															
		IHD								not IHD							
		MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
		NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM	NS	SM
Surviving co-twin	NS	4	0	6	0	0	0	10	0	19	4	35	3	1	1	55	8
	SM	2	2	1	2	0	0	3	4	2	5	6	4	0	0	8	9

SM=Smoker; NS=Non Smoker

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MZ twins who died from IHD were cigarette smokers as against 80 % of their surviving co-twins. Counting only present smokers (Table 26), the corresponding figures are 30 % vs 80 %. Smoking >10 cigarettes daily is significantly ($p < 0.05$) more common among the surviving male MZ co-twins, whose partners died from IHD, than among their counterparts whose partners died from other causes; this is true for present smokers (50 % vs 4 %) and for present and former smokers combined (50 % vs 8 %). The corresponding comparisons between the deceased male MZ co-twins give the same trend but it is not so pronounced. However, with regard to the larger group of death discordant male DZ pairs, there is a higher proportion of cigarette smokers among the surviving co-twins whose partners died from other causes (50 %) compared to those whose partners died from IHD (36 %), but among their deceased partners the proportions are about the same (41 % vs 40 %).

Of the female twins who died from IHD (Table 28), 24 % were smokers compared with 41 % of their surviving co-twins, while the corresponding figures for the not-IHD death discordant twins are 21 % and 21 %. Nearly all the female smokers were cigarette smokers. Of the former smokers, only one was found among the deceased co-twins. None of the differences recorded among the females is statistically significant.

Smoking discordance among the male death discordant pairs is shown in Tables 29-30. Only among the DZ twin pairs in whom death discordance was not caused by IHD is there an apparant smoking discordance: in 7 of the smoking discordant pairs the surviving co-twins were smokers compared to 4 pairs in which the deceased twins were smokers. If only cigarette smoking discordant pairs are considered, the corresponding figures for the not-IHD death discordant pairs were 5 and 3. Nor were there statistically significant differences among the females with respect to smoking discordance (Table 31).

<u>Comments</u>

With regard to mortality from IHD, especially in men, most studies indicate a positive relation to smoking (Doll & Hill, 1964; Best, 1966; Hammond, 1966; Kannel, 1966; Fletcher & Horn, 1970). The present number of smoking discordant twin pairs among the IHD death discordant pairs is too small to permit an evaluation of the effect of smoking on IHD mortality, but it can be mentioned that in the mortality study on the whole of the Swedish Twin Registry (Friberg et al, 1973), a hypermortality, partly due to IHD, was found among DZ smoking discordant pairs but not among MZ pairs in both men and women. It may well be that cigarette smoking only reflects a certain constitution and that

SM=Smoker; NS=Non Smoker

smokers and non-smokers are self-selected groups. This view is also supported by the twin studies by Lundman (1966) and Liljefors (1970). Examining 196 twin pairs with different intra-pair smoking habits, Lundman found no difference in IHD manifestations between the more and less exposed twins. In the male twin pairs studied by Liljefors, smoking habits did not differ appreciably in pairs discordant with regard to the probable presence of IHD. Neither did life-time exposure, expressed as cigarette years, show any association with IHD. Nor was there any difference in smoking exposure in the infarction discordant pairs.

The findings of proportionally more cigarette smokers among the surviving male MZ co-twins whose partners died from IHD compared to those whose partners died from other causes could indicate an association between cigarette smoking and IHD. The larger male DZ group did not show similar differences in cigarette smoking habits. However, the deceased male MZ twins also displayed the same trend in cigarette smoking habits as the surviving co-twins, which may indicate that it is constitutional factors which lie behind these findings.

ALCOHOL

Studies on the association between alcohol consumption and IHD have yielded conflicting results. Chronic alcoholics have been considered to possess protection from coronary atherosclerosis. Several authors (e.g. Grant et al, 1959; Stare, 1961; Biörck, 1963) found no association between alcohol consumption and IHD. Data from the Framingham study support the opinion that alcohol is not correlated with IHD (Kannel, 1966) - alcohol consumption apparently showed no association with the development of IHD, neither did it protect against atherosclerosis of the heart.

In a mortality study on approximately one million persons under the age of 50, alcoholism and heavy drinking were overrepresented among fatal IHD cases (Bainton et al, 1963). A study from Norway has also shown a higher mortality from IHD among chronic alcoholics compared to the general population (Sundby, 1967). In a report on men born in 1913, registration at the local temperance board showed a strong association with mortality in myocardial infarction (Tibblin, 1972).

Material: see Chapter I.

Table 32. Distribution of death discordant male twin pairs according to registration in Alcohol Registry.

IHD								not IHD							
MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S

Table 32. Distribution of death discordant male twin pairs according to registration in Alcohol Registry.

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Registered	1	0	5	3	1	2	7	5	6	8	19	15	0	0	25	23
Total number	10	10	25	25	5	5	40	40	25	25	42	42	1	1	68	68

D=Deceased twin; S=Surviving co-twin

Table 33. Distribution of death discordant male twin pairs according to concordance/discordance with respect to registration in Alcohol Registry.

		Deceased twin															
		IHD								not IHD							
		MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
		NR	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR	R
Surviving co-twin	NR	9	1	18	4	2	1	29	6	15	2	16	11	1	0	32	13
	R	0	0	2	1	2	0	4	1	4	4	7	8	0	0	11	12

R=Registered; NR=Not Registered

Methods

Persons with alcohol problems were defined operationally as those entered in a nationwide registry for misconduct while under the influence of alcoholic beverages. This registry has existed since 1932. All the male death discordant twins were matched with the registry.

Results

The numbers of death discordant male twins with entries in the Alcohol Registry are shown in Table 32. Entries were found for 32 out of 108 (30 %) deceased twins compared to 28 out of 108 (26 %) surviving co-twins. Of the 40 twins who had died from IHD, 7 (18 %) had been registered compared with 5 of their surviving partners (13 %), whereas of the 68 who had died from other causes than IHD, 25 (37 %) had been registered compared with 23 of their surviving partners (34 %). A distribution of the registered twins in the death discordant pairs (Table 33) shows that only one of the IHD death discordant pairs, a DZ pair, is concordant with respect to registration compared to 12 in the not-IHD group. Among the discordant (registered/not registered) pairs there are no significant differences within the death discordant pairs.

Comments

An entry in the Alcohol Registry usually indicates that the person in question has alcohol problems. It was found by Helander (1972), that 11.5 % of male twins born 1900-1924 had at least one conviction for drunkenness compared to only 0.2 % of the female twins, the corresponding figure for male twins born 1925-1954 being 11.3 % and for females 0.6 %. Because so few female twins have been registered, only male twins were matched with the Alcohol Registry. A mortality follow-up of 9,000 twin pairs from the Swedish Twin Registry has shown entry in the Alcohol Registry to be associated with a higher mortality regardless of smoking and it was also found that 10 % of non-smokers were registered as against 30 % of those who smoked more than 10 cigarettes a day (Friberg et al, 1973). Concerning the cause-specific death rates, a weak association was found between registration and IHD. In the present investigation too, registration was somewhat more common among the deceased twins irrespective of the cause of death (IHD/not IHD). However, alcohol registration does not seem to have contributed to the high prevalence of IHD manifestations in the surviving co-twins in the IHD death discordant pairs. Using questionnaire replies in 1967 concerning

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alcohol consumption, Myrhed (1974) investigated 70 male twin pairs discordant with respect to alcohol consumption. The alcohol discordant pairs did not differ in IHD manifestations evaluated as ST depressions in connection with exercise. A check of the questionnaire replies from 1967/1970 on alcohol consumption for the present material yielded a fairly high proportion of non respondents (27 % among the deceased male twins and 36 % among their surviving co-twins, compared to 44 % among the deceased female twins and 46 % among their surviving co-twins), which is why this source of information on alcohol consumption could not be used here.

PHYSICAL INACTIVITY AND SOME SOCIAL FACTORS

Physical inactivity or sedentary living has also been implicated as a risk factor for IHD (Simborg, 1970; Karvonen, 1972; Stamler, 1973). The findings are not as clearcut or consistent as for many other risk factors, probably due to the difficulty of defining. Results from the Health Insurance Plan (Frank et al, 1966) and the Framingham study (Kannel, 1966) have shown a striking increase of fatal myocardial infarction among physically inactive men. No such correlation was found to angina pectoris and coronary insufficiency in the Framingham study but the Health Insurance Plan showed angina pectoris to be even more common in the more active group of men. The Western collaborative study (Frank et al, 1966) has also confirmed that regular exercise habits were less common among those with a fatal as opposed to a non-fatal myocardial infarction. On the other hand, the seven countries study (Keys et al, 1970) disclosed no association between the incidence of IHD and physical inactivity in any of the cohorts. It is also worth noting that the members of the cohorts from Finland had the highest incidence of IHD but were usually the most physically active and non-obese.

Various social and psychosocial factors have been considered as risks for IHD (cf. Jenkins, 1971). The complexity of these variables and the lack of uniform methods for their investigation make such studies difficult to perform and evaluate. Stamler (1973) considers the modern way of life in highly urbanized societies to play an important role in the causation of IHD.

Results differ with regard to the correlation of different socio-economic groups to IHD (Hofvendahl & Helmers, 1973). A higher prevalence of myocardial infarction has been noted among employers,

especially owners of small shops and salesmen (Biörck et al, 1958). Analyses of later studies have tended instead towards a higher prevalence and incidence of IHD in the lower socio-economic groups (Antonowsky, 1968).

A low educational background has also been associated with an increased risk of myocardial infarction (Antonowsky, 1968; Hinkle, 1969). Social group mobility (Wardwell, 1968) as well as occupational mobility (Syme, 1964) are other sociologic factors which have been found to discriminate IHD patients from other subjects.

According to Friedman & Rosenman (1959), individuals exhibiting an emotional complex characterized by an excessive sense of time urgency, drive, and competitiveness (type A behavior) are more prone to the onset of IHD than are individuals of the converse type of behavior (type B). Type A subjects usually have elevated cholesterol values and are also more often heavy smokers than type B subjects. Other psychosocial characteristics found in men with myocardial infarction seem to be job dissatisfaction (Sales & House, 1971; Theorell, 1971), and overtime work (Kasanen et al, 1963; Liljefors, 1970).

Material: see Chapter I.

Methods

Information on physical inactivity and some social factors (change of place of work, extra work and place of residence) was obtained from questionnaires mailed to all twins in 1967 and 1970, while information on education was obtained from questionnaires in 1962. The twins were asked among other things if they had changed their place of work after the age of 25 and how often, if they had had extra work beside their ordinary job and if this happened ⩾ periodically. They were also asked about their place of residence after the age of 25 and if this had been mostly in big cities. Higher education is taken here to be education above the compulsory school, including folk-high school, vocational school and evening courses. The twins were also asked about how much exercise they had taken when 25-50 years of age; the answer "hardly any" was recorded here.

Results

The distribution of death discordant pairs according to their answers on physical inactivity and various sociologic variables is given in Tables 34 and 35. Hardly any ecercise when 25-50 years of age is

Table 34. Physical inactivity and some sociologic variables in the male death discordant pairs according to earlier questionnaires. Absolute numbers and prevalence rates in % (parenthesis).

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Hardly any exercise	2	1	6	6	0	0	8	7	3	2	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(20)	(10)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]								

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Table 34. Physical inactivity and some sociologic variables in the male death discordant pairs according to earlier questionnaires. Absolute numbers and prevalence rates in % (parenthesis).

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Hardly any exercise	2 (20)	1 (10)	6 (24)	6 (24)	0 (0)	0 (0)	8 (20)	7 (18)	3 (12)	2 (8)	4 (10)	5 (12)	0 (0)	0 (0)	7 (10)	7 (10)
Change of place of work ≥5 times	0 (0)	0 (0)	0 (0)	2 (8)	3 (60)	1 (20)	3 (8)	3 (18)	4 (16)	4 (16)	6 (14)	3 (7)	0 (0)	0 (0)	10 (15)	7 (10)
Extra work	3 (30)	3 (30)	14 (56)	13 (52)	1 (20)	0 (0)	18 (45)	16 (40)	12 (48)	15 (60)	18 (43)	24 (57)	0 (0)	0 (0)	30 (44)	39 (57)
Place of residence Mostly big cities	0 (0)	1 (10)	4 (16)	3 (12)	1 (20)	1 (20)	5 (13)	5 (13)	4 (16)	2 (8)	7 (17)	10 (24)	1 (100)	1 (100)	12 (18)	13 (19)
Higher education	4 (40)	3 (30)	3 (12)	2 (8)	3 (60)	3 (60)	10 (25)	8 (20)	2 (8)	6 (24)	12 (29)	9 (21)	1 (100)	0 (0)	15 (22)	16 (24)
Total number	10	10	25	25	5	5	40	40	25	25	42	42	1	1	68	68

D=Deceased twin; S=Surviving co-twin

Table 35. Physical inactivity and some sociologic variables in the female death discordant pairs according to earlier questionnaires. Absolute numbers and prevalence rates in % (parenthesis).

	IHD								not IHD							
	MZ		DZ		XZ		Tot.		MZ		DZ		XZ		Tot.	
	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Hardly any exercise	2 (25)	0	1 (11)	0	-	-	3 (18)	0	2 (7)	1 (3)	5 (10)	7 (15)	0	0	7 (9)	8 (10)
Change of place of work ≥5 times	1 (13)	0	0	0	-	-	1 (6)	0	2 (7)	2 (7)	1 (2)	2 (4)	0	0	3 (4)	4 (5)
Extra work	2 (25)	0	1 (11)	3 (33)	-	-	3 (18)	3 (18)	5 (17)	8 (27)	15 (31)	16 (33)	0	0	20 (25)	24 (30)
Place of residence Mostly big cities	0	0	0	0	-	-	0	0	7 (23)	4 (13)	9 (19)	10 (21)	0	0	15 (19)	15 (19)
Higher education	2 (25)	2 (25)	2 (22)	1 (11)	-	-	4 (24)	3 (18)	7 (23)	7 (23)	10 (21)	10 (21)	0	1 (50)	17 (21)	18 (23)
Total number	8	8	9	9			17	17	30	30	48	48	2	2	80	80

D=Deceased twin; S=Surviving co-twin

reported slightly more often among the IHD death discordant male pairs than among the not-IHD death discordant pairs (20 % vs 18 % compared to 10 % vs 10 %). Among the IHD death discordant female twin pairs, 3 (18 %) of the deceased twins had reported hardly any exercise vs none of the surviving co-twins. With regard to change of place of work, extra work and place of residence, there are no substantial differences between the surviving and the deceased twins in the IHD death discordant male and female pairs. None of the female twins in the IHD death discordant pairs had mostly lived in big cities, whereas this applied to 19 % in the not-IHD group. With regard to higher education (above compulsory school), the proportion of educated subjects is much the same in the IHD and not-IHD male death discordant pairs but there are more marked differences within the various zygosity groups. Among the female IHD death discordant pairs the proportion of twins with higher education is 24 % vs 18 % compared to 21 % vs 23 % in the not-IHD group. None of the differences is statistically significant.

Comments

The sociologic data in the present study concern factors which may possibly predispose for IHD. However, precipitating factors, such as various life changes, have been shown to precede the onset of myocardial infarction (Theorell, 1971) and sudden death (Rahe & Lind, 1971) but the accumulation of life changes prior to the onset of disease does not seem to be a specific sign for IHD (Rahe, 1969).

To judge from the results of this study, it does not seem very likely that the social factors recorded could be responsible for the increased prevalence of IHD manifestations in the surviving co-twins in the IHD death discordant pairs. In the twin study by Liljefors (1970), ambition and overtime work were noted significantly more often among the affected partners in the infarction discordant MZ pairs.

It should be born in mind, however, that in retrospective studies the diseased subjects often tend to be more aware of signs and symptoms associated with the disease in question.

4. COMBINATION OF FACTORS ASSOCIATED WITH ISCHAEMIC HEART DISEASE AMONG THE SURVIVING CO-TWINS

Prospective epidemiological studies have demonstrated the highest risk of developing IHD in subjects with multiple "risk factors" (Dawber et al. 1957; Kannel et al, 1961; Kannel et al, 1967; Tibblin & Wilhelmsen, 1971; Böttiger & Carlson, 1972; Stamler & Epstein, 1972). Data from the Pooling Project in the U.S.A. (Stamler & Epstein, 1972) show that the risk of death in IHD for white males aged 30-59 increased fivefold if they had three of the major risk factors (serum cholesterol $\geq$250 mg/dl; diastolic blood pressure $\geq$90 mm Hg; cigarette smoking). In the Stockholm Prospective Study, male subjects with 4 "risk factors" (any four of cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, hemoglobin and cigarette smoking) had a 10 times higher risk of developing a myocardial infarction.

Material: see Chapter II.

Methods

Before combining "risk factors" it is necessary to define "risk levels" for each factor. The methods for this are described in the presentation of the separate factors. The following "risk factors" and "risk levels" have been used:

1) Relative weight $\geq$110.
2) Basal systolic blood pressure $\geq$160 mm Hg and/or basal diastolic blood pressure phase 4 $\geq$95 mm Hg; or on antihypertensive treatment and not reaching the defined blood pressure levels.
3) Cholesterol $\geq$250 mg/100 ml and/or triglycerides $\geq$150 mg/100 ml; or on lipid reducing drugs and not reaching the defined lipid levels.
4) Diabetes mellitus: history of clinical diabetes mellitus.
5) Cigarette smoking: present cigarette smoking as elucidated from the mailed questionnaire 1967/1970.
6) Physical inactivity: hardly any exercise during 25-50 years of age as elucidated from the mailed questionnaire 1967/1970.
7) Extra work: Extra work $\geq$periodically beside the regular job as elucidated from the mailed questionnaire 1967/1970.

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Results

The distribution of surviving co-twins according to the number of certain defined biometric "risk factors" (the possible combinations of the four factors defined under Methods) is presented in Table 36 and visualized in Fig. 8. The male co-twins whose partners died from IHD have on average 1.3 "risk factors" as compared to 1.2 among the co-twins whose partners died from other causes. Among the men whose partners died from IHD, the MZ co-twins have more "risk factors" than the DZ co-twins (1.6 vs 1.3) and the same trend applies among the men whose partners died from other causes (1.4 vs 1.1). The female co-twins have on average proportionally more biometric "risk factors" but the trends in the differences between zygosity groups are about the same as in the males.

In Table 37 and Fig. 9, three environmental factors, defined under Methods, are also included in the possible combination of "risk factors". None of the co-twins had all the "risk factors" but six of them were noted for one male MZ co-twin whose partner died from IHD.

The environmental factors contribute proportionally less to the increased number of risk factors per person among the females. The male MZ co-twins whose partners died from IHD now have on average 2.8 "risk factors" per person, mainly due to the relatively high proportion of present cigarette smokers. However, comparisons between the pooled male zygosity groups (IHD/not IHD) show fairly close agreement in prevalence rates throughout the different numbers of "risk factors". Among the women it is worth noting that the MZ co-twins, whose partners died from IHD, recorded only one of the environmental factors, which explains the reverse difference here between MZ and DZ co-twins within the IHD group.

Tables 38-39 display the cumulative distribution of the number of biometric as well as biometric plus environmental "risk factors". Of the male co-twins whose partners died from IHD, 80 % have at least one biometric risk factor as compared to 69 % of those whose partners died from other causes. The corresponding figures among the females are 94 % and 85 %. When environmental factors are also included in the combination, nearly all the twins have at least one "risk factor". There are two or more biometric "risk factors" in 40 % of the male co-twins with partners who died from IHD and in 38 % of those whose partners died from other causes. Among the females the corresponding figures are 82 % and 56 %. Including the environmental "risk factors", 73 % and 75 % of the male co-twins have at least two "risk factors", and 88 % and 71 % of the females.

Table 36. Distribution of respondent co-twins according to number of certain defined biometric "risk factors".

	MALES								FEMALES							
	IHD				not IHD				IHD				not IHD			
Number of factors	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)
0	2 (20)	4 (16)	2 (40)	8 (20)	5 (20)	16 (38)	0	21 (31)	0	1 (11)	-	1 (6)	4 (13)	8 (17)	0	12 (15)
1	3 (30)	11 (44)	2 (40)	16 (40)	10 (40)	11 (26)	0	21 (31)	1 (13)	1 (11)	-	2 (12)	8 (27)	15 (31)	0	23 (29)
2	3 (30)	8 (32)	1 (20)	12 (30)	5 (20)	11 (26)	1 (100)	17 (25)	3 (38)	4 (44)	-	7 (41)	9 (30)	14 (29)	0	23 (29)
3	1 (10)	2 (8)	0	3 (8)	4 (16)	4 (10)	0	8 (12)	4 (50)	3 (33)	-	7 (41)	9 (30)	10 (21)	2 (100)	21 (26)
4	1 (10)	0	0	1 (3)	1 (4)	0	0	1 (1)	0	0	-	0	0	1 (2)	0	1 (1)
Factors/co-twin	1.6	1.3	0.8	1.3	1.4	1.1	2.0	1.2	2.4	2.0	-	2.2	1.8	1.6	3.0	1.7
Numbers of co-twins	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

Table 37. Distribution of respondent co-twins according to number of certain defined biometric and environmental "risk factors".

	MALES								FEMALES							
	IHD				not IHD				IHD				not IHD			
Number of factors	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)

Table 37. Distribution of respondent co-twins according to number of certain defined biometric and environmental "risk factors".

Number of factors	MALES IHD MZ No. (%)	MALES IHD DZ No. (%)	MALES IHD XZ No. (%)	MALES IHD Tot. No. (%)	MALES not IHD MZ No. (%)	MALES not IHD DZ No. (%)	MALES not IHD XZ No. (%)	MALES not IHD Tot. No. (%)	FEMALES IHD MZ No. (%)	FEMALES IHD DZ No. (%)	FEMALES IHD XZ No. (%)	FEMALES IHD Tot. No. (%)	FEMALES not IHD MZ No. (%)	FEMALES not IHD DZ No. (%)	FEMALES not IHD XZ No. (%)	FEMALES not IHD Tot. No. (%)
0	0	0	1 (20)	1 (3)	0	3 (7)	0	3 (4)	0	0	-	0	4 (13)	2 (4)	0	6 (8)
1	2 (20)	7 (28)	1 (20)	10 (25)	3 (12)	11 (26)	0	14 (21)	1 (13)	1 (11)	-	2 (12)	3 (10)	14 (29)	0	17 (21)
2	4 (40)	7 (28)	3 (60)	14 (35)	12 (48)	14 (33)	0	26 (38)	3 (38)	3 (33)	-	6 (35)	8 (27)	12 (25)	0	20 (25)
3	1 (10)	8 (32)	0	9 (23)	6 (24)	9 (21)	1 (100)	16 (24)	3 (38)	3 (33)	-	6 (35)	11 (37)	12 (25)	2 (100)	25 (31)
4	1 (10)	2 (8)	0	3 (8)	3 (12)	4 (10)	0	7 (10)	1 (13)	2 (22)	-	3 (18)	3 (10)	7 (15)	0	10 (13)
5	1 (10)	1 (4)	0	2 (5)	1 (4)	1 (2)	0	2 (3)	0	0	-	0	1 (3)	1 (2)	0	2 (3)
6	1 (10)	0	0	1 (3)	0	0	0	0	0	0	-	0	0	0	0	0
Factors/co-twin	2.8	2.3	1.4	2.3	2.5	2.1	3.0	2.2	2.5	2.7	-	2.6	2.3	2.2	3.0	2.3
Number of co-twins	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

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Table 38. Respondent co-twins tabulated according to the cumulative distribution of certain defined biometric "risk factors".

Number of "risk factors"	MALES IHD MZ No. (%)	MALES IHD DZ No. (%)	MALES IHD XZ No. (%)	MALES IHD Tot. No. (%)	MALES not IHD MZ No. (%)	MALES not IHD DZ No. (%)	MALES not IHD XZ No. (%)	MALES not IHD Tot. No. (%)	FEMALES IHD MZ No. (%)	FEMALES IHD DZ No. (%)	FEMALES IHD XZ No. (%)	FEMALES IHD Tot. No. (%)	FEMALES not IHD MZ No. (%)	FEMALES not IHD DZ No. (%)	FEMALES not IHD XZ No. (%)	FEMALES not IHD Tot. No. (%)
≥1	8 (80)	21 (84)	3 (60)	32 (80)	20 (80)	26 (62)	1 (100)	47 (69)	8 (100)	8 (89)	-	16 (94)	26 (87)	40 (83)	2 (100)	68 (85)
≥2	5 (50)	10 (40)	1 (20)	16 (40)	10 (40)	15 (36)	1 (100)	26 (38)	7 (88)	7 (78)	-	14 (82)	18 (60)	25 (52)	2 (100)	45 (56)
≥3	2 (20)	2 (8)	0	4 (10)	5 (20)	4 (10)	0	9 (13)	4 (50)	3 (33)	-	7 (41)	9 (30)	11 (23)	2 (100)	22 (28)
≥4	1 (10)	0	0	1 (3)	1 (4)	0	0	1 (1)	0	0	-	0	0	1 (2)	0	1 (1)
≥5	0	0	0	0	0	0	0	0	0	0	-	0	0	0	0	0
Number of co-twins	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

Table 39. Respondent co-twins tabulated according to the cumulative distribution of certain defined biometric and environmental "risk factors".

Number of "risk	MALES IHD MZ	MALES IHD DZ	MALES IHD XZ	MALES IHD Tot.	MALES not IHD MZ	MALES not IHD DZ	MALES not IHD XZ	MALES not IHD Tot	FEMALES IHD	FEMALES not IHD

Table 39. Respondent co-twins tabulated according to the cumulative distribution of certain defined biometric and environmental "risk factors".

Number of "risk factors"	MALES IHD MZ No. (%)	MALES IHD DZ No. (%)	MALES IHD XZ No. (%)	MALES IHD Tot. No. (%)	MALES not IHD MZ No. (%)	MALES not IHD DZ No. (%)	MALES not IHD XZ No. (%)	MALES not IHD Tot. No. (%)	FEMALES IHD MZ No. (%)	FEMALES IHD DZ No. (%)	FEMALES IHD XZ No. (%)	FEMALES IHD Tot. No. (%)	FEMALES not IHD MZ No. (%)	FEMALES not IHD DZ No. (%)	FEMALES not IHD XZ No. (%)	FEMALES not IHD Tot. No. (%)
≥ 1	10 (100)	25 (100)	4 (80)	39 (98)	25 (100)	39 (93)	1 (100)	65 (96)	8 (100)	9 (100)	-	17 (100)	26 (87)	46 (96)	2 (100)	74 (93)
≥ 2	8 (80)	18 (72)	3 (60)	29 (73)	22 (88)	28 (67)	1 (100)	51 (75)	7 (88)	8 (89)	-	15 (88)	23 (77)	32 (67)	2 (100)	57 (71)
≥ 3	4 (40)	11 (44)	0	15 (38)	10 (40)	14 (33)	1 (100)	25 (37)	4 (50)	5 (56)	-	9 (53)	15 (50)	20 (42)	2 (100)	37 (46)
≥ 4	3 (30)	3 (12)	0	6 (15)	4 (16)	5 (12)	0	9 (13)	1 (13)	2 (22)	-	3 (18)	4 (13)	8 (17)	0	12 (15)
≥ 5	2 (20)	1 (4)	0	3 (8)	1 (4)	1 (2)	0	2 (3)	0	0	-	0	1 (3)	1 (2)	0	2 (3)
≥ 6	1 (10)	0	0	1 (3)	0	0	0	0	0	0	-	0	0	0	0	0
≥ 7	0	0	0	0	0	0	0	0	0	0	-	0	0	0	0	0
Number of co-twins	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

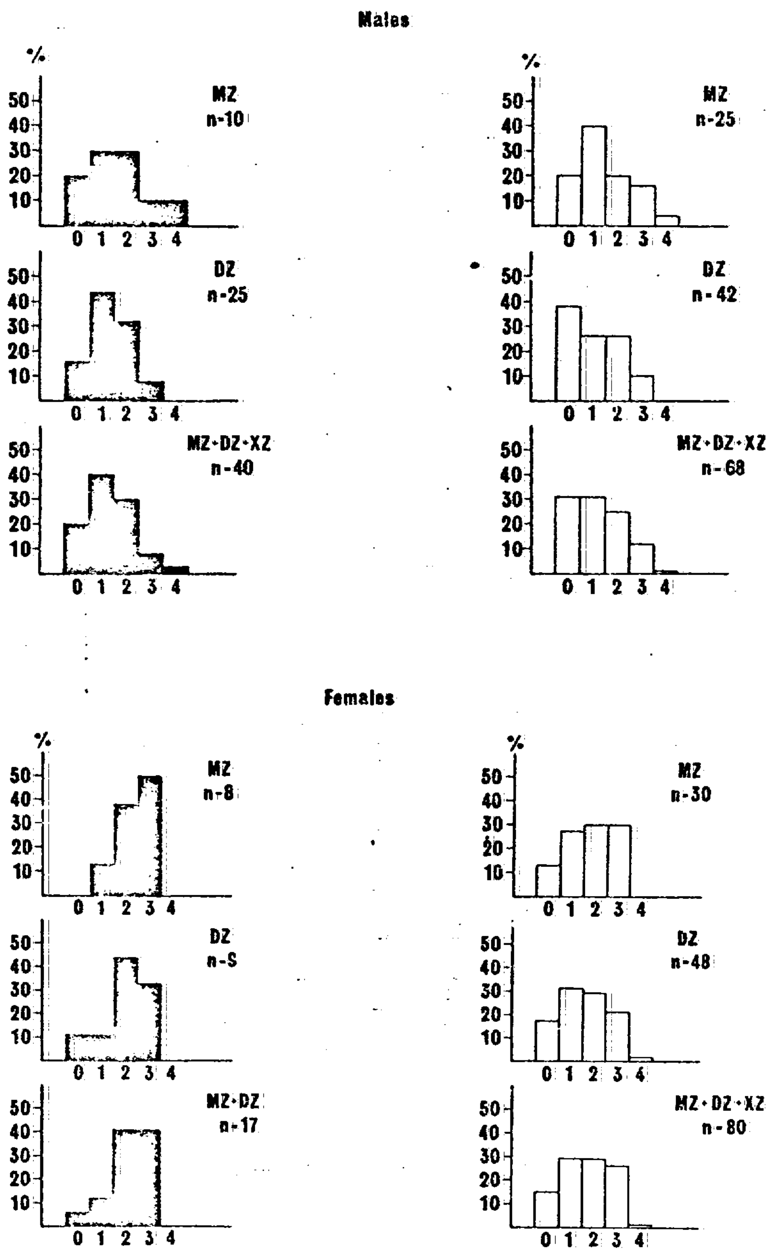

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Fig. 8. Distribution of respondent co-twins according to certain defin biometric "risk factors". Black columns indicate that the partners die from IHD and white columns that the partners died from other causes.

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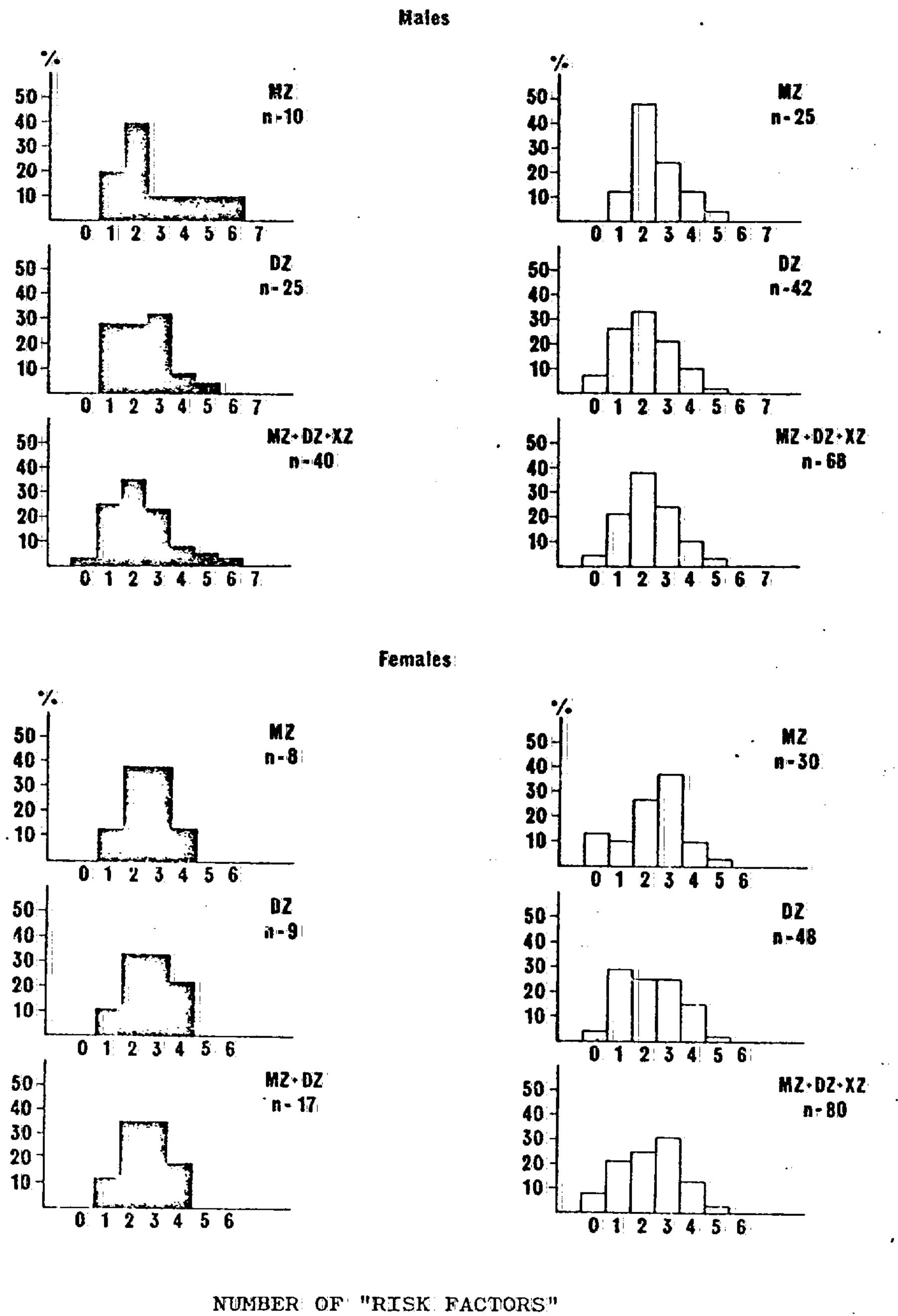

Fig. 9. Distribution of respondent co-twins according to certain defined biometric and environmental "risk factors". Black columns indicate that the partners died from IHD and white columns that the partners died from other causes.

None of the differences with regard to the number of risk factors is statistically significant.

Comments

Before combining "risk factors" it is necessary to define "risk levels" for each factor. The cut-off points used here have been chosen fairly liberally, which naturally increases the sensitivity but decreases the specificity with regard to the risk of IHD. It seems, however, that the risk rises steadily from the lowest to the highest values for most of the continuous risk factors (Dawber & Kannel, 1972; Stamler & Epstein, 1972).

New statistical methods for multivariate analyses have been applied more recently to evaluate the risk of IHD when several risk characteristics are considered simultaneously. In the Framingham study, a multiple logistic model was used to compute risk probabilities for each individual (Truett et al, 1967). Coefficients for each of the risk factors were based on the risk factor level at the first examination and the 12-year IHD incidence.

The relative importance of risk factors is, however, not the same in all populations. Furthermore, the multivariate risk functions have not yet been translated into clinical terms. A combination of risk factors defined by arbitrarily chosen levels can therefore be useful as a broad classification of high risk individuals.

In the present study, the number of risk factors does not differ significantly between co-twins whose partners died from IHD and those whose partners died from other causes. When only biometric risk factors were combined, the same tendencies are found for both males and females with more risk factors among the MZ than the DZ co-twins, irrespective of the cause of death of the partner (IHD/notIHD). Furthermore, the co-twins with partners who died from IHD have somewhat more risk factors than those whose partners died from other causes, the difference being more pronounced among the females.

Twin studies cited in connection with the separate risk factors have shown that the biometric risk factors are governed to varying degrees by heredity but may also be influenced by the environment. In a prospective study of 50-year-old men in Gothenburg, the occurrence of risk factors had a predictive value not only for the incidence of myocardial infarction but also for early death from other causes (Tibblin, 1972). The differences in number of risk factors between MZ and DZ co-twins irrespective of the cause of death of the partner might thus reflect constitutional differences. The male co-twins with partner

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who died from IHD have rather more biometric risk factors than those whose partners died from other causes but the difference is not very marked, possibly because the so-called risk factors are not as specific for IHD as used to be thought. According to Tibblin (1972), some common factor such as premature aging could be responsible for an increased number of risk factors as well as the development of myocardial infarction and death from non-cardiovascular causes.

The differences in the number of biometric risk factors show the same trends when environmental risk factors (cigarette smoking, physical inactivity and extra work) are included in the possible combination. The environmental factors, however, contributed proportionally less to the increased number of factors among females, especially the MZ co-twins whose partners died from IHD, than among the males. Harvald & Hauge (1968), in their study on Danish twin pairs, found the occurrence of fatal "coronary occlusion" to be genetically determined to a much larger extent in females than males. They considered environmental factors to play a greater part in the etiology of IHD in males compared to females.

In a comparison between male and female populations in Gothenburg with respect to risk factors for IHD (Bengtsson et al, 1973), it was concluded that sex differences in these factors apparently explain only part of the different incidences of myocardial infarction in men and women. Smoking, alcohol consumption and stress experience were, however, more common among the males.

The present differences in the number of risk factors do not significantly discriminate the surviving co-twins with partners who died from IHD and those whose partners died from other reasons, which partly could be due to a lack of specificity in the risk factors. The tendencies, however, are consistent with a somewhat higher number of risk factors among the co-twins whose partners died from IHD. The slight differences in the number of risk factors may reflect different constitutions but it is also probable that genetic factors operate independently of the established risk factors in the development of IHD. Firmer conclusions in this respect will have to await a mortality follow-up of the examined co-twins.

IV

GENERAL DISCUSSION

Epidemiological studies have indicated that IHD has a multifactorial etiology. From the standpoint of preventive action, most interest has been focused on the environmental factors, which can be modified and controlled, and there have been relatively few studies on the importance of familial factors and the genetic predisposition for IHD, which seem to be especially important for detecting individuals at highest risk. Twin studies probably offer the best tool with which to study the relative influence of genetic and environmental factors.

Various theoretical models in twin studies were discussed at an international twin symposium in Puerto Rico in 1969 but it was also pointed out that there is no generally accepted methodology in the design of twin studies and that the possibilities are many and complex. It was suggested that clinical examination of the partners of twins who have died could be considered as a valuable extension of mortality studies.

One of the main purposes of the present study is to evaluate a genetic influence in IHD - by examining whether the occurrence of IHD in the surviving co-twin is associated with the partner's cause of death (IHD/not IHD).

The present material of death discordant pairs comprises 78.2 % of a sample selected from the Swedish Twin Registry. This response rate must be considered fairly high, partly because the population was drawn from the whole of Sweden and partly in view of the fact that the co-twins had lost their partners on average 5 months earlier.

The accuracy of cause of death determinations depends mainly on a high autopsy rate. Because the autopsy rate for the deceased twins in the present material was about 57 %, other sources of information (hospital records etc.) were consulted in order to make the mortality evaluation as reliable as possible.

This was especially important because the IHD material included cases of sudden death (ISC number 795.99). If there was a strong suspicion that a case of sudden death had some other explanation than IHD as the underlying cause, then it was not included in the IHD group. About 70 % of the sudden deaths included as IHD cases had either a preexisting history of IHD (myocardial infarction and/or angina pector on effort) or findings at autopsy indicating IHD (signs of fresh or ol infarct and/or severe atherosclerotic changes of the coronary arteries as compared to about 4 % of the twins who died from other causes than

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IHD. The other 30 % of the IHD sudden deaths had no such earlier evidence of this disorder; they were included because there was no other reasonable explanation for the death. This is in line with other studies, in which the initial clinical manifestation of IHD was found to be sudden death in about 20-25 % of IHD cases (Kuller et al, 1966; Kuller, 1966). In the present investigation, analyses of the occurrence of IHD and risk factors among the surviving co-twins have been related to the cause of death of the partner (IHD, not IHD). In addition to the cases of sudden death, the IHD death discordant pairs thus include those where the cause of death was myocardial infarction. Pooling these two diagnoses, as has been done in many epidemiological studies, seems to be justifiable not only because about 70 % of the sudden deaths showed evidence of previous IHD but also because the risk factors for the sudden death cases are in general agreement with those for myocardial infarction (Vedin et al, 1973). Neither did the relatively small number of IHD death discordant pairs permit a further breakdown into subgroups.

The occurrence of IHD in the surviving co-twins was established by determining the prevalence of angina pectoris, myocardial infarction and ECG changes suggestive of IHD. Angina pectoris and myocardial infarction was found more commonly among the surviving co-twins whose partners died from IHD than among those whose partners died from other causes. Among females this was true for angina pectoris. The trend was clearest with regard to myocardial infarction among males but none of the differences is statistically significant. The relatively low prevalence of manifest IHD in conjunction with the small numbers of MZ and DZ co-twins makes it difficult to assess the significance of heredity. According to Epstein (1964), a prevalence rate of 5.5 % for manifest IHD represents only the "top of the iceberg". It has been considered that ST depressions in connection with exercise could be a fairly sensitive and specific predictor of coronary obstructive disease (Helfant et al, 1973). The appearance of ST segmental depressions in response to exercise has been shown to be a powerful predictor of overt IHD (Mattingly, 1962; Åstrand & Lundman, 1968; Blackburn et al, 1970; Doyle & Kinch, 1970). Using ST depressions in connection with exercise as a sign of IHD among the surviving co-twins, the frequency among both the male and the female co-twins whose partners died from IHD was significantly higher than among the co-twins whose partners died from other causes. In the males the difference was significant for ST depressions ≥ 1 mm but in the females only when ST depressions of ≥ 0.5 mm were included. These differences certainly reflect constitutional differences. The impression of a substantial genetic influence in IHD is strengthened

by the finding that the male MZ co-twins whose partners died from IHD displayed significantly more IHD manifestations than those MZ co-twins whose partners died from other causes despite the fact that the group with partners who died from IHD was about 5 years younger.

It is well known that ST depressions seem to be a less specific sign of IHD in women (Biörck, 1946; Lepeschkin, 1958; Åstrand, 1965). They were more common among the females than among the males in the present study and did not discriminate the genetically predisposed individuals from the others as effectively as among the males. It has been conjectured that ECG changes suggestive of IHD in women may reflect hypertension rather than IHD (Bengtsson, 1973). It is thus conceivable that the relatively high blood pressure, especially the casual, in the female co-twins whose partners died from IHD, accounts to some extent for the difference in IHD manifestations. This possibility is strengthened by the fact that if one excludes ST depressions accompanied by high R-wave amplitudes (code 3:1), which are thought to reflect a left ventricular hypertrophy due to hypertension, then the differences in the females are no longer significant. It must, however, be born in mind that the level of blood pressure has been shown by some authors (Takkunen, 1964; Lundman, 1966) to be under a relatively strong genetic influence, so that the differences with regard to IHD manifestations in the females could also reflect constitutional differences. In the Framingham study, electrocardiographic evidence of left ventricular hypertrophy was strongly associated with both hypertension and IHD; when the criteria for left ventricular hypertrophy included ST depression and T-wave inversion, IHD incidence was predicted over and above what could be accounted for by the concurrent hypertension (Kannel et al, 1970; Dawber & Kannel, 1972). It was suggested that these abnormalities reflect, in addition to hypertensive hypertrophy, an ischaemic myocardial involvement due to associated coronary atherosclerosis.

One of the other purposes of the present investigation was to study whether there is an association between the risk factor profile of the surviving co-twin and the partner's cause of death (IHD/not IHD). For this purpose the factors found to be associated with IHD were divided into biometric and environmental. It is probable that the determinants of many of the biometric factors are mostly genetic but they may be susceptible to environmental influence, too. Similarly environmental factors may be linked in some measure with the genetic constitution (Biörck, 1959).

For most of the separate biometric risk factors recorded, the values were consistently somewhat higher among both the male and the

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female co-twins whose partners died from IHD, compared to those whose partners died from other causes and this was especially true for the MZ co-twins. It must be remembered, however, that the zygosity groups differ somewhat in age, which could possibly affect the interpretation of the results. The male MZ co-twins whose partners died from IHD were on average nearly 5 years younger than both the DZ co-twins in the same IHD group and the MZ co-twins whose partners died from other causes than IHD.

Furthermore, the male DZ co-twins with IHD partners were about 4 years older than those whose partners had not died from IHD. As some of the biometric risk factors are more or less age dependent, it is thus possible that the differences between the MZ co-twins are somewhat underestimated, whereas the reverse is true for the DZ co-twins. However, the pooled male zygosity groups (IHD/not IHD) had about the same mean age. There was also an age difference among the females, the MZ and DZ co-twins whose partners died from IHD being about 4 years older than the corresponding co-twins whose partners died from other reasons. It is thus possible that the differences found with respect to, for instance, blood pressure and cholesterol are to some extent due to the difference in age.

Concerning the environmental factors, except alcohol registration, information was obtained from questionnaires mailed to all twins in the Swedish Twin registry in the years 1967 and 1970. At that time, all the present death discordant pairs were unbroken. It seemed advisable to use the information in earlier questionnaires because the death of the partner might have distorted answers from surviving co-twins as well as those obtained through relatives about the deceased partners.

With regard to smoking, alcohol registration, physical inactivity and some social factors, no substantial differences were found between the deceased and the surviving twins in the death discordant pairs. The IHD death discordant pairs included a somewhat higher proportion of total smokers as well as cigarette smokers, compared to the not-IHD death discordant pairs, and the proportion of cigarette smokers was especially high among the male IHD death discordant MZ pairs (60 % among the deceased partners and 80 % among the survivors).

Most epidemiological studies point to a positive relation, especially in men, between mortality in IHD and smoking (Doll & Hill, 1964; Best, 1966; Hammond, 1966; Kannel, 1966; Fletcher & Horn, 1970). No association was found in the present investigation but it must be born in mind that the numbers involved are small. The surviving MZ and XZ male co-twins whose partners died from IHD were cigarette

smokers, especially ≥ 11 cigarettes daily, proportionally more often than the other male MZ and XZ twins, a circumstance which may have contributed to the corresponding difference in IHD manifestations. However, the deceased MZ and XZ twins also displayed the same tendencies in the smoking of cigarettes. Thus it is possible that the differences with regard to cigarette smoking merely reflect differences in constitution, which could play the major part also with regard to the development of IHD.

Among the men born in 1913 (Tibblin, 1972), it seemed that being registered with the local temperance board was strongly associated with myocardial infarction. All the male death discordant twins in the present investigation have been matched against a register for misconduct involving alcohol. Registration was somewhat more common, although not significantly so, among the deceased twins, irrespective of the cause of death (IHD/not IHD).

The questionnaire data used in this study on sociologic background variables represent factors which could predispose for IHD. These findings, however, do not preclude the operation of precipitating factors such as various life changes, which have been shown to precede the onset of myocardial infarction (Theorell, 1971) and sudden death (Rahe & Lind, 1971).

The highest risk of developing IHD has been demonstrated among individuals with multiple "risk factors" (Dawber et al, 1957; Kannel et al, 1961; Kannel et al, 1967; Tibblin & Wilhelmsen, 1971; Böttiger & Carlson, 1972; Stamler & Epstein, 1972). The risk factors used in the combination were defined with fairly liberal cut-off points, which is a practical and common way of defining risk levels. Risk evaluation by means of new statistical methods for multivariate analyses seems to be a more physiological approach, considering that the risk steadily increases from the lowest to the highest values for most of the continuous variables (Dawber & Kannel, 1972; Stamler & Epstein, 1972). These methods have not yet been translated into clinical terms and the coefficients for each of the risk factors are based upon special populations. Using a multivariate risk function (Wilhelmsen et al, 1973) based on the variables cholesterol, systolic blood pressure and smoking, it has been shown (Elmfeldt, 1974) that a fairly high proportion of men developed myocardial infarction notwithstanding their classification as "low risks".

When only biometric risk factors were combined in the present study, more risk factors were noted among the MZ co-twins than the DZ co-twins, irrespective of the cause of death (IHD/not IHD). The same trend was found when the environmental risk factors (cigarette

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smoking, physical inactivity and extra work) were included in the possible combination. The environmental factors contributed proportionally less to the increase in the number of risk factors among the females, especially the MZ co-twins whose partners died from IHD, than among the males. Environmental factors have been found to play a less important role in the development of IHD in women (Harvald & Hauge, 1968; Bengtsson, 1973). The differences found in the number of risk factors did not significantly discriminate the surviving co-twins whose partners died from IHD from those whose partners died from other reasons, a circumstance which could be due to an insufficient specificity of the risk factors. Incidence data from the prospective study on men born in 1913 (Tibblin, 1972) have shown that most of the risk factors which have been considered to be rather specific for the subsequent occurrence of myocardial infarction also appear to be almost as valid for early death from whatever cause.

To judge from the results of the present study, it can be concluded that a considerable genetic influence seems to operate in the development of IHD. Genetic influences are transmitted through some of the established risk factors, but it is possible that unknown risk factors or a general biologic factor as "premature ageing" (Tibblin, 1972) or low "life potential" (Biörck, 1974) constitute the most important underlying factor in the development of IHD. Dawber & Kannel (1972) have proposed, that the continued high morbidity and mortality from IHD could be a consequence of ageing and genetic make-up and that the important factors contributing to the development of this disease have not been identified satisfactorily. It has also been proposed by Epstein (1964) that if one could identify and measure all of the predisposing traits as underlying biologic disturbances in terms of metabolic or other defects, then it would probably emerge that they are more common than the prevalence of the disease would suggest and show more clear-cut distributions among family members. It was furthermore concluded that the prevention of IHD demands that the carriers of these traits be identified, so that prophylactic measures can be instituted at an early age among genetically susceptible individuals.

V

GENERAL SUMMARY AND CONCLUSIONS

All the twins in the Swedish Twin Registry have been the subject of a continuous mortality follow-up ever since the Registry was established in 1959-1961. The complete twin registry is matched regularly against a total death registry for Sweden at the Central Bureau of Statistics and this procedure makes it possible to obtain the death certificates. Since 1971 the matching has been done every month. This procedure was a prerequisite for the present study.

The principal object of this investigation was to evaluate the genetic influence in IHD in the examined co-twins and to create a basis for their further mortality follow-up, thereby also paving the way for assessments of the predictive value of the measured risk factors and the hereditary influence.

All unbroken male and female twin pairs from the Swedish Twin Registry below the age of 70 who, in the period January 1st, 1971 to March 15th, 1973, became death discordant, were selected for the study. 78.2 % or 205 of the surviving co-twins could be examined on average about 5 months after the death of the partner.

The cause of death of the partner was established by a team of physicians on the basis of all the assembled information (hospital records, autopsy protocols etc.). The causes of death were classified according to the International Statistical Classification of Diseases.

The zygosity diagnoses were taken from the record in the Twin Registry, which is based upon questions as to similarity. If the twins in a pair had given conflicting answers, they were classified as unknown zygosity (XZ).

Among 108 male death discordant pairs, the cause of death was IHD in 40 pairs (10 MZ, 25 DZ and 5 XZ) and other than IHD in 68 pairs (25 MZ, 42 DZ and 1 XZ). Among 97 female death discordant pairs, the cause of death was IHD in 17 pairs (8 MZ, 9 DZ) and other than IHD in 80 pairs (30 MZ, 48 DZ and 2 XZ).

191 of the surviving co-twins were examined at the Seraphimer Hospital and the other 14 at their local hospital.

A sociologic and medical history was taken, using questionnaires. The diagnosis of angina pectoris was established by interview according to the questionnaire designed by the London School of Hygiene and Tropical Medicine. Myocardial infarction was considered established when it had been verified at hospital. Blood pressure determinations, anthropometric measurements and X-ray of the heart and lungs were

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performed as well as ECG before, during and after an ergometer test. Blood samples were drawn after an overnight's fast for analyses of cholesterol, triglycerides, uric acid and blood sugar. Erythrocyte sedimentation rate, hemoglobin and hematocrit were also determined. The urine was tested for proteinuria and glucosuria.

Myocardial infarction had occurred in 15 % of the surviving male co-twins whose partners had died from IHD (3 or 30 % of the MZ co-twins and 3 or 12 % of the DZ co-twins) as compared to only 3 % of the surviving co-twins whose partners had died from other causes than IHD. Only one of the female co-twins had had myocardial infarction. If angina pectoris, pathologic Q-wave and segmental ST depressions $\geqslant 0.5$ mm in connection with exercise were also included in the criteria of IHD, both male and female co-twins (pooled zygosity groups) whose partners died from IHD displayed these signs significantly ($p < 0.05$) more often than those whose partners died from other causes. In the males, but not in the females, the difference was significant even when ST depressions $\geqslant 1.0$ mm was included in the criteria of IHD. Similarly, the male MZ co-twins whose partners died from IHD displayed significantly more IHD manifestations ($p < 0.05$ with ST depressions $\geqslant 1.0$ mm, and $p < 0.01$ with ST depressions $\geqslant 0.5$ mm) than the MZ co-twins whose partners had died from other causes. Excluding ST depressions coded in the presence of high R-wave amplitudes (Minnesota code 3:1), which are thought to reflect a left ventricular hypertrophy due to hypertension, the differences in the females are no longer significant.

Most of the biometric factors measured (relative weight, skinfold thickness, blood pressure, lipids, uric acid) showed somewhat higher values for the co-twins whose partners died from IHD compared to those whose partners died for other reasons. The difference in casual systolic blood pressure was significant ($p < 0.05$) among the females. Overt diabetes mellitus showed about the same prevalence in the two death discordant groups (IHD, not IHD). Nor were significant differences found with regard to hematocrit, hemoglobin or erythrocyte sedimentation rate, which some authors have designated as "risk factors" for IHD. Information obtained earlier through mailed questionnaires about smoking habits, physical inactivity, extra work, change of place of work, education and place of residence, did not significantly discriminate the deceased and the surviving co-twins. The IHD death discordant pairs had a somewhat higher proportion of smokers (83 % vs 85 %) compared to the not-IHD (76 % vs 72 %). To smoke $\geqslant 11$ cigarettes daily was significantly ($p < 0.05$) more common among the surviving male MZ co-twins whose partners died from IHD than among those whose partners died from other causes. The corresponding comparison between

the deceased male MZ co-twins gave the same trend but not so pronounced.

All male death discordant twins were matched against a nationwide register for misconduct while under the influence of alcohol. Registration was more common among the not-IHD death discordant pairs. The deceased partners had been registered somewhat more often, irrespective of the cause of death (IHD, not IHD).

The biometric "risk factors" (relative weight $\geqslant 110$ according to a height-weight index, basal systolic blood pressure $\geqslant 160$ mm Hg and/or basal diastolic blood pressure $\geqslant 95$ mm Hg, cholesterol $\geqslant 250$ mg/100 ml and/or triglycerides $\geqslant 150$ mg/100 ml, and overt diabetes mellitus) were then combined with the environmental "risk factors" (cigarette smoking, extra work and physical inactivity). It was found that the surviving co-twins whose partners died from IHD had on average a somewhat higher number of biometric risk factors than those whose partners died from other causes, the difference being more pronounced among the female co-twins. The inclusion of environmental "risk factors" contributed proportionally less to the number of "risk factors" among the females, especially the MZ co-twins.

The conclusions from the present investigation could be summarized as follows:

1) The present results indicate a substantial genetic influence in the development of IHD.

2) In males the risk factors measured, singly and in combination, seem to explain only part of the difference in IHD manifestations between the surviving co-twins whose partners died from IHD and those, whose partners died from other causes. In females, however, elevated blood pressure may explain a great deal of the difference found in IHD manifestations. The genetic influences are probably transmitted not only through some of the risk factors measured but also through factors which are still unknown.

3) The environmental factors recorded by earlier questionnaires did not discriminate significantly between the deceased and the surviving co-twins.

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Adapt

Q and QS pa

(Do not

1.1.1 Q/R am

1.1.2 Q durat

1.1.3 Q durat

1.1.4 Q durat

1.1.5 Q durat

1.1.6 QS patt

1.1.7 QS patt

1.2.1 Q/R am leads I.

1.2.2 Q durat

1.2.3 QS patt

1.2.4 Q durat amplitu

1.2.5 Q durat

1.2.6 Q ampli

1.2.7 QS patte

1.2.8 R amplit CR_2 an

1.3.1 Q/R am 0.03 sec

1.3.2 QS patt

1.3.3 Q durat

1.3.4 Q durat amplitu

1.3.5 Q durat

1.3.6 QS patt

ST depressions

(Do not

4.1 ST-J dep or 1.0 m and ST s

4.2 ST-J dep horizont

4.3 ST-J dep horizonta

4.4 No ST-J reaching

4.5 No ST-J sloping

4.6 Isolated or 1.0 m ST segme

4.7 Isolated or 0.5-0. ST segme

APPENDIX

The "Minnesota code" for ECG classification.
Adaptation to CR (CH) leads and modification of the code for ECGs recorded during and after exercise.

<u>Q and QS patterns</u>

(Do not code in presence of ventricular conduction defects 6.4 or 7.1)

1.1.1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 sec. or more in any of leads I, II, $CR_{2,3,4,5,6,7}$.

1.1.2 Q duration 0.04 sec. or more in any of leads I, II, $CR_{1,2,3,4,5,6,7}$.

1.1.3 Q duration 0.04 sec. or more plus R amplitude of 3 mm or more in lead aVL.

1.1.4 Q duration 0.05 sec. or more in lead III plus any Q wave of at least 1.0 mm amplitude in aVF.

1.1.5 Q duration 0.05 sec. or more in lead aVF.

1.1.6 QS pattern when R wave is present in adjacent lead to the right on the chest in any of leads $CR_{2,3,4,5,6,7}$.

1.1.7 QS pattern in all of leads CR_1 through $CR_{4,5,6}$ or 7.

1.2.1 Q/R amplitude ratio 1/3 or more plus Q duration at least 0.02 sec. and less than 0.03 sec. in any of leads I, II, $CR_{2,3,4,5,6,7}$.

1.2.2 Q duration at least 0.03 sec. and less than 0.04 sec. in any of leads I, II, $CR_{2,3,4,5,6,7}$.

1.2.3 QS pattern in lead II.

1.2.4 Q duration of at least 0.04 sec. and less than 0.05 sec. in lead III plus any Q wave of at least 1.0 mm amplitude in aVF.

1.2.5 Q duration at least 0.04 sec. and less than 0.05 sec. in lead aVF.

1.2.6 Q amplitude of 5 mm or more in either of leads III, aVF.

1.2.7 QS pattern in all of leads CR_1 through CR_3.

1.2.8 R amplitude decreasing to 2.5 mm or less, and absence of codes 3.2, 7.2 or 7.3 between any of leads CR_2 and CR_3, CR_3 and CR_4, CR_4 and CR_5, CR_5 and CR_6 or CR_6 and CR_7.

1.3.1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 sec. and less than 0.03 sec. in any of leads I, II, $CR_{2,3,4,5,6,7}$.

1.3.2 QS pattern in absence of code 3.1, in each of leads CR_1 and CR_2.

1.3.3 Q duration of at least 0.03 sec. and less than 0.04 sec. plus R amplitude of 5 mm or more in lead aVL.

1.3.4 Q duration of at least 0.03 sec. and less than 0.04 sec. in lead III plus any Q wave of at least 1.0 mm amplitude in lead aVF.

1.3.5 Q duration of at least 0.03 sec. and less than 0.04 sec. in lead aVF.

1.3.6 QS pattern in each of leads III and aVF.

<u>ST depressions</u>

(Do not code in presence of ventricular conduction defects 6.4, 7.1,2,4)

4.1	ST-J depression of 1.5 mm or more	CR_{2-7}
	or 1.0 mm or more	I, II, aVL, aVF
	and ST segment straight and slowly ascending, horizontal or downward sloping	
4.2	ST-J depression of 1.0-1.4 mm and ST segment straight and slowly ascending, horizontal or downward sloping	CR_{2-7}
4.3	ST-J depression of 0.5-0.9 mm and ST segment straight and slowly ascending,	CR_{2-7}
	horizontal or downward sloping	I, II, aVL, aVF
4.4	No ST-J depression as much as 0.5 mm but ST segment downward sloping and	CR_{2-7}
	reaching 0.5 mm or more below P-R baseline	I, II, aVL, aVF
4.5	No ST-J depression as much as 0.5 mm but ST segment horizontal or downward	CR_{2-7}
	sloping but reaching less than 0.5 mm below P-R baseline	I, II, aVL, aVF
4.6	Isolated ST-J depression of 1.5 mm or more	CR_{2-7}
	or 1.0 mm or more,	I, II, aVL, aVF
	ST segment upward sloping	
4.7	Isolated ST-J depression of 0.5-1.4 mm or more	CR_{2-7}
	or 0.5-0.9 mm or more	I, II, aVL, aVF
	ST segment upward sloping	

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